

WHAT IS CLAIMED IS:

1. A method for the analysis of mixtures containing proteins, said method comprising the steps of:

- (a) reducing the disulfide bonds in the proteins of a sample, thereby providing thiol groups in cysteine-containing proteins;
- (b) blocking free thiols with a blocking reagent in the sample;
- (c) digesting the proteins in the sample to provide peptides;
- (d) reducing the disulfide bonds in the digested peptides, thereby providing thiol groups in cysteine-containing peptides for reaction;
- (e) reacting cysteine-containing peptides in the sample with a reagent, wherein said reagent comprises a thiol-specific reactive group which is attached to a polymer tag via a linker, wherein the linker can be differentially labeled with stable isotopes and wherein the polymer tag forms a covalent bond with the cysteine-containing peptides;
- (f) washing the polymer-bound peptides to remove non-covalently bound species;
- (g) eluting the cysteine-containing peptides; and
- (h) subjecting the eluted peptides to quantitative mass spectrometry (MS) analysis.

2. The method according to claim 1, wherein said method further comprises the steps of:

- performing steps (a) to (d) on a second sample;
- reacting cysteine-containing labels in the second sample with a stable isotope-labeled form of the reagent, wherein in reacting step (e), the reagent used is a non-isotope labeled form the reagent;
- mixing the peptides of the reacted sample following step (e) and the reacted second sample; and
- performing steps (g) and (h) on the peptides in the mixture.

3. The method according to claim 1, wherein the reagent comprises a thiol-specific reactive group is selected from the group consisting of  $\alpha$ -haloacetyl and maleimide.



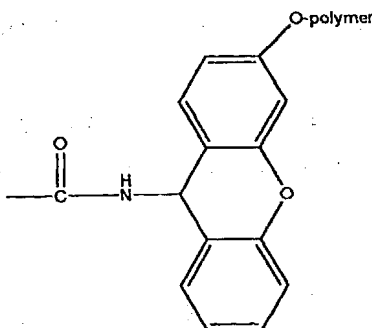
4. The method according to claim 1, wherein the blocking reagent is methyl methane thiosulfonate.

5. The method according to claim 1, wherein the reagent has the formula:

A1 - Linker - A2 - polymer

wherein A1 is the thiol-reactive group and A2 is an acid labile group to which the polymer is bound.

6. The method according to claim 5, wherein the acid-labile group bound to the polymer has the structure:



7. The method according to claim 5, wherein the polymer in the reagent is a polymer resin.

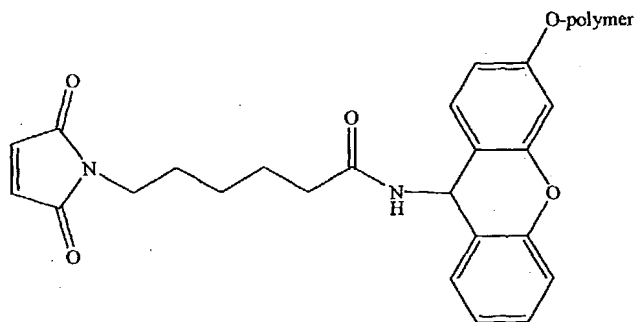
8. The method according to claim 7, wherein the polymer resin is a homopolymer or heteropolymer comprising a polymer selected from the group consisting of polystyrene and polyethylene glycol.

9. The method according to claim 8, wherein the linker contains a substitution of at least six hydrogen atoms with a stable isotope.

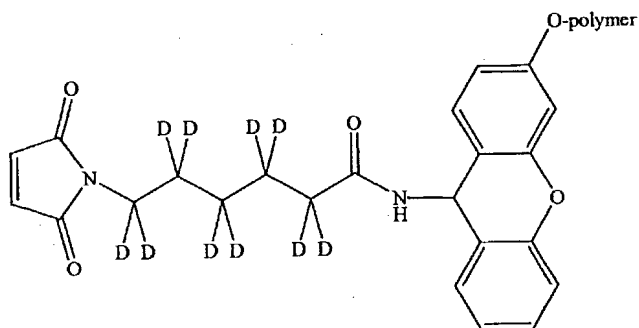
10. The method according to claim 9, wherein the linker contains ten stable isotopes.

11. The method according to claim 9, wherein the stable isotope is deuterium.

12. The method according to claim 1, wherein the non-isotope-labeled reagent is

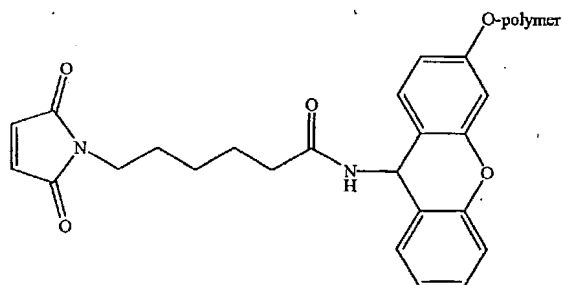


- (13) The method according to claim 1, wherein the isotope labeled reagent has the formula:

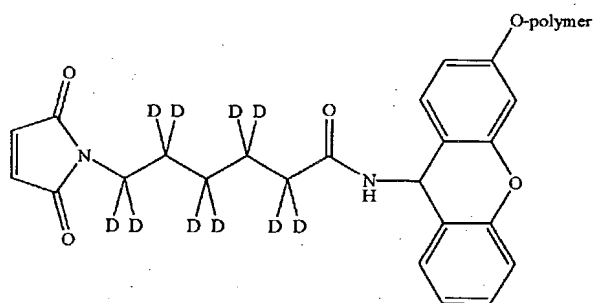


14. The method according to claim 1, wherein the eluted peptides are subjected to high-performance liquid chromatography-mass spectrometry (MS) analysis, two-dimensional liquid chromatography MS, or MS/MS analysis.
15. The method according to claim 1, wherein the proteins are digested using trypsin.
- (16) A compound useful for capturing cysteine-containing peptides, which is selected from the group consisting of a thiol-specific reactive group attached to a non-biological polymer via a linker.
17. The compound according to claim 16, wherein the linker contains a substitution of at least six atoms with a stable isotope.
18. The compound according to claim 16, wherein the linker contains ten stable isotopes.
19. The compound according to claim 17, wherein the stable isotope is deuterium.

20. The compound according to claim 16, selected from the group consisting of:



and



21. A reagent kit for the analysis of proteins by mass spectral analysis that comprises a compound of claim 16.

22. The reagent kit of claim 21 which comprises a set of substantially identical differentially labeled cysteine-tagging reagents.

23. The reagent kit of claim 22 further comprising one or more proteolytic enzymes for use in digestion of proteins to be analyzed.